

Final Report
on

CONTRACT No. N6onr-225, T.O. VIII
NR 112/250

Fred A. Hitchcock
June 15, 1953

**THE OHIO STATE UNIVERSITY
RESEARCH FOUNDATION**

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Report No. FINAL
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R E P O R T

by

THE OHIO STATE UNIVERSITY
RESEARCH FOUNDATION

Columbus 10, Ohio

Cooperator: OFFICE OF NAVAL RESEARCH
Contract No. N6onr-225, T.O. VIII
NR 112 250

Investigation of: GASEOUS EXCHANGES IN THE PULMONARY ALVEOLI

Subject of Report: Final for the period
1 January 1947 to 31 August 1952

Submitted by: Fred A. Hitchcock

Date: June 15, 1953

FINAL REPORT
ONR Contract N6onr-225, T.O. VIII
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As the result of work done on the sudden reduction of barometric pressure (explosive decompression) during World War II, it occurred to us that such sudden reduction of the ambient pressure might be used as a direct method of measuring lung volume. For instance, if a subject makes a maximal exhalation and then maintains his thoracic cage in this position while the ambient pressure is explosively reduced to one-half its initial value, we may assume in accordance with Boyle's law that the air in the lungs would expand to double its initial volume and that one-half of this increased volume would escape through the mouth and nose. This seemed to offer a method of not only measuring directly the volume of residual air contained in the lungs but also of determining its composition since samples could be analyzed after the air had been collected in a spirometer and the volume measured. A series of experiments was carried out in this way. However, the results invariably showed that the volume obtained by this method was larger than that obtained when the standard dilution method of measuring lung volume was used. Furthermore, when the air expelled from the lungs during explosive decompression was analyzed, it was found that its composition varied considerably from that of alveolar air which was collected immediately before explosive decompression. The chief differences in composition were a marked increase in the percentage of both CO_2 and O_2 present. The most logical explanation of these observed differences in volume and composition lay in the assumption that the alveolar air tended to come into equilibrium with the new ambient pressure during the time that the air was escaping from the lungs. Thus

we may assume that the reduction of the ambient pressure with its concurrent decrease in $p\text{CO}_2$, $p\text{O}_2$ and $p\text{H}_2\text{O}$ would result in the rapid diffusion of all three of these gases from the blood into the alveolar air of the lungs. This process would account for the excessive increase in volume as well as for the change in composition. Since our publication of this method, it has been developed at Randolph Field and is now in use there for the measurement of lung volume.

From such considerations as this, it became apparent to us that the technique for producing explosive decompression which had been developed in the Ohio State University Laboratory of Aviation Physiology made available a new method for the investigation of respiratory problems. In January 1947, a contract was entered into between the Office of Naval Research and The Ohio State University Research Foundation for the continuation and expansion of this line of investigation. It seemed to us that the successful prosecution of this problem required an instrument which would rapidly and continuously analyze air expelled from the lungs. After an extensive review of the literature and consultation with authorities from other laboratories, including Dr. A. O. Nier of the University of Minnesota, we reached the conclusion that a specially constructed mass spectrometer was the instrument which gave the greatest promise of meeting our specifications and requirements. Since no instrument such as we visualized was available commercially, it became evident that it would be necessary for us to construct a mass spectrometer of the type required in our own laboratory. There was considerable delay in obtaining personnel and materials required for such an ambitious project. In the meantime, we made various attempts to mechanically fractionate and collect the air

expelled from the lungs during explosive decompression. Early attempts were valueless due to the fact that the dead space of the apparatus was so great as to make it impossible to obtain undiluted samples of the air expelled from the lungs. The mechanical fractionating device which was developed in this early work is shown in Figures 1 and 2. The apparatus consists of a rotating disc by means of which apertures connected by rubber tubing to a series of small spirometers are consecutively brought into position opposite the mouthpiece through which the subject is exhaling. In order to avoid dilution of the samples for analysis with the air of the dead space of the apparatus, samples consisting of the last air expelled in each fraction were taken by means of a hypodermic needle inserted through the rubber tubing close to the mouthpiece and connected to a sampling tube. In this way a sample of the last air expelled from the lungs in each fraction was taken for analysis. The use of this mechanical device, however, was never considered satisfactory and attention was concentrated on the development of the mass spectrometer.

The construction of this instrument was well advanced by the end of the first year of the project. It was constructed on the general principle developed and published by A. O. Nier. This mass spectrometer made possible the simultaneous analysis of oxygen, nitrogen and carbon dioxide. By means of a special calibrating arrangement, quantitative determination of all three of these gases was possible. A continuous record of results obtained on all three gases could be made on a single photographic film. The time required for a full-scale change in concentration was less than .2 second and the analytical error less than 2% of the full-scale deflection.

A description of the apparatus was published in The Review of Scientific Instruments, Volume 20, No. 5, pp 333-336, May 1949.

Following the completion of the mass spectrometer, work was initiated to determine the role of various factors concerned in determining the composition of alveolar air. The time required for the establishment of equilibrium in the alveoli of the lungs following a rapid drop in barometric pressure was measured. The results obtained indicate that the new equilibrium is completely established by the time the last of the expanding air escapes from the lungs. When the composition of the inspired air was suddenly changed it was determined that the time required for the establishment of the new equilibrium depended upon the rapidity with which the lungs were ventilated with the air of different composition. The results indicated that this usually required about ten complete respiratory cycles. The composition of expired air was also continuously determined. Results obtained indicated that when the last of the dead space air was being exhaled there was a slight decrease in the pO_2 which probably resulted from dilution with water vapor. The pO_2 then fell rapidly and gradually leveled off but never reached a plateau. While the pO_2 was dropping the pCO_2 rose even more rapidly than the pO_2 dropped. The pCO_2 then gradually leveled off, but continued to rise slowly as long as exhalation continued. Thus it was found that the final value for the pO_2 and the pCO_2 was a function of the duration of the exhalation. The longer the exhalation lasted the lower the pO_2 and the higher the pCO_2 . The fact that the pCO_2 rose more rapidly than the pO_2 dropped resulted in a high R. Q. at the beginning of the exhalation. This R. Q. then fell progressively as the exhalation continued. The R. Q. value obtained near the

end of the exhalation was the value which agreed most nearly with the R.Q. of the exhaled air.

The ratio of CO_2 produced to O_2 absorbed calculated from a small fraction of the air expelled in a single exhalation can in no sense be considered a metabolic R. Q. In fact, it seems desirable to avoid the use of this term when referring to such a ratio. In this laboratory we have used the term "Air Quotient" (A.Q.) to denote this relationship. However, it is possible that the symbol "R" as recommended in 1950 by the Committee on Standardization of Definitions and Symbols in Respiratory Physiology to denote respiratory exchange ratio ($\text{vol CO}_2/\text{vol O}_2$) might be the more appropriate method of expressing this concept.

During the progress of this work a number of technical difficulties arose with the instrument which necessitated frequent modifications and on one or two occasions a complete overhauling. Much of the trouble centered in the DC amplifiers used. In the meantime plans were developed for the construction of a smaller and simpler mass spectrometer which it was hoped would be of value in clinical investigations.

After having demonstrated the variations in alveolar pCO_2 that regularly occur during individual respiratory cycles, it seemed logical to attempt to find similar variations in pulmonary venous blood. Because of the nature of the oxygen dissociation curve, it seemed unlikely that the small differences in pO_2 would result in significant changes in oxygen content of the pulmonary venous blood. However, the CO_2 content of this blood might very well be expected to exhibit consistent and significant changes that could be correlated with the changes in pCO_2 of alveolar air. A technique was devised by which samples of blood from the pulmonary veins could be obtained at various phases of the respiratory cycle. These

experiments were carried out with open thorax and during artificial respiration. Samples of blood were drawn immediately following the inflation of the lungs and again just before the beginning of deflation. In this way we avoided any change in lung volume during the drawing of samples. The CO_2 content of the blood samples was determined by means of the Van Slyke manometric blood gas apparatus. In every case the CO_2 content of the second sample was greater than that of the first. The mean difference was about 3.2 volumes per cent. There was no significant difference in the O_2 content of these samples. These experiments are open to criticism on the grounds that they were carried out during artificial respiration and that the individual respiratory cycles were of somewhat longer duration than would be expected during spontaneous breathing. Furthermore, there is evidence which indicates that such changes in pulmonary venous blood are more easily obtained in dogs than in man. For these reasons it would be desirable to repeat these experiments during spontaneous breathing and, if possible, with human subjects. The collection of blood samples from the pulmonary veins in human beings represents a problem which would be difficult to solve.

Another group of experiments was undertaken for the determination of respiratory dead space by means of the mass spectrometer. Since this instrument records almost instantaneously the CO_2 content of exhaled air, it is a simple matter to place a flow meter in the stream of exhaled air and, with the help of the mass spectrometer, determine the volume of air which was exhaled before any noticeable increase in the CO_2 content of the exhaled air occurred. In these experiments human subjects were used. They were in a sitting position on a bicycle ergometer. They breathed through

a conventional mouthpiece arranged with flutter valves which permitted air flow in only one direction. The hypodermic needle which served as an inlet to the mass spectrometer was placed in the mouthpiece 3 to 5 mm from the subject's lips. The out flow from the mouthpiece was connected to a flow meter which consisted of a sintered brass disc. Differential pressures on the two sides of the disc were measured and recorded by means of a rubber tambour manometer. The deflections of this tambour were recorded optically on the same photographic paper as that used in recording the deflections of the mass spectrometer. Experiments were run in which the subjects (1) breathed normally while sitting at rest (2) hyperventilated voluntarily and (3) exercised violently on the bicycle ergometer. The results obtained in these experiments with the mass spectrometer were compared with the determination of dead space calculated in the conventional way. As might be expected, the mass spectrometer method gave slightly lower values than did the conventional method. This undoubtedly results from the fact that the mass spectrometer method measures the volume of air which is unmixed with alveolar air. On the other hand, the dead space air as measured conventionally includes that portion of the inspired air which is mixed with alveolar air as well as the air which was completely unchanged in composition. These experiments have not been published as yet and it is felt that the method justifies additional work along this line.

In association with Dr. Ralph W. Stacy, Arthur B. Chilton, Commander in the Civil Engineering Corps of the U. S. Navy, has worked out mathematical analyses of the carbon dioxide excretion in man. The stimulus for this work was the demonstration of the dynamic nature of the variations of alveolar $p\text{CO}_2$ as shown in records obtained with the mass spectrometer. This

analysis was carried out by means of physical-mathematical models and resulted in the derivation of formulas which make possible the analysis of the external carbon dioxide respiration in man under conditions of metabolic equilibrium. The methods evolved are flexible, permitting study of a wide variety of physiological assumptions. Simple calculations relate various factors in the process of external respiration and show good agreement with experimental data. A quantitative description of the effects of various factors on rate of carbon dioxide output and alveolar tension is given. In particular, this theory gives a quantitative prediction of the fluctuation in alveolar carbon dioxide tension over the period of a single respiratory cycle. This work has been published in the Bulletin of Mathematical Biophysics, Volume 14, pages 1-18, 1952, a reprint of which is included with this report.

During the final year of work on this contract, several new investigations were initiated.

1. An investigation was begun on the variations which occur in alveolar air with changes in posture. This work has not yet been completed.

2. Work was initiated on the composition of the residual air in the lungs of animals at ambient pressures lower than the vapor pressure of body fluids. Since there is a rapid evaporation of body fluids at such pressures, it seemed desirable to be able to determine water vapor by means of the mass spectrometer; therefore, an attempt was made to modify this instrument in such a way as to make it possible to record the percentage of water vapor present in the gases studied. This would also make possible the determination of the composition of gases which accumulate in subcutaneous spaces following explosive decompression to such extremely low pressures.

3. The mass spectrometer was also used to study the changes in the composition of alveolar air which occurred during artificial respiration, particularly when the Seeler valve was used.

4. A new, small portable mass spectrometer was constructed with a view to its use in the clinic. This instrument has not yet been completed.

During the four years that this contract was active, the following

graduate students wrote theses and dissertations based on research done under this contract:

Ralph W. Stacy, Ph.D. dissertation, "Studies of the Dynamic Behavior of Lung Gases and of Gas Tensions of Alveolar Air Following Sudden Change of Partial Pressure of Oxygen in Inspired Air."

George H. Kydd, III, Master's thesis, "Studies on the Composition of Expired Air Made by Means of a Mass Spectrometer."

Rene C. Mastrovito, Master's thesis, "Study of the Behavior and Characteristics of a Mass Spectrometer with a Cold Cathode Type Ion Source".

John T. Rodgers, Master's thesis, "Studies of Water Vapor Content of Respired Air."

The following papers and abstracts based on research done under this contract have been published:

A New Technique for Respiration Analysis, Monthly Research Report of the Office of Naval Research, November 1951.

A Mathematical Analysis of Carbon Dioxide Respiration in Man, Bulletin of Mathematical Biophysics, Volume 14, 1952.

A Mass Spectrometer for Continuous Gas Analysis, The Review of Scientific Instruments, Vol. 20, No. 5, pp. 333-336, May 1949.

Determination of Water Vapor Pressure of Respired Air by Electrochemical Means, American Journal of Physiology, Vol. 163, Dec 1950.

Determination of Respiratory Dead Space Made by Means of a Mass Spectrometer, The American Journal of Physiology, Vol. 163, No. 3, Dec 1950.

New Techniques for Respiration Analysis, The Graduate School Record, Vol. 5, No. 4, Jan 1952.

Dynamic Effects of Low Oxygen Tensions of Inspired Air on Alveolar Gas Tensions, Journal of Applied Physiology, Vol. 5, No. 11, May 1953. (Reprints will be forwarded to ONR when available.)

Variation of Respiratory Quotient During Normal and Deep Exhalation, Federation Proceedings, Vol. 9, No. 1, March, 1950

Mass Spectrographic Studies on Expired and Alveolar Air, Federation Proceedings, Vol. 8, No. 1, March, 1949

Factors Affecting the Composition of Alveolar Air, American Journal of Physiology, Vol. 155, No. 3, Dec. 1948

Respiratory Variation of O_2 and CO_2 Content of Pulmonary Vein Blood,
American Journal of Physiology, Vol. 163, Dec 1950.

NOTE: In submitting this report it is understood that all provisions of
the contract between The Foundation and the Cooperator and pertain-
ing to publicity of subject matter will be rigidly observed.

Investigator.....*James C. Wolpert*.....Date *17 June 1953*

.....*for the W.R.H.*.....

Supervisor.....*Frank H. Stetson*.....Date *17 June 1953*

.....
For The Ohio State University Research Foundation

Executive Director...*Oram C. Wolpert*.....Date *15 June 1953*.....
W.R.H.

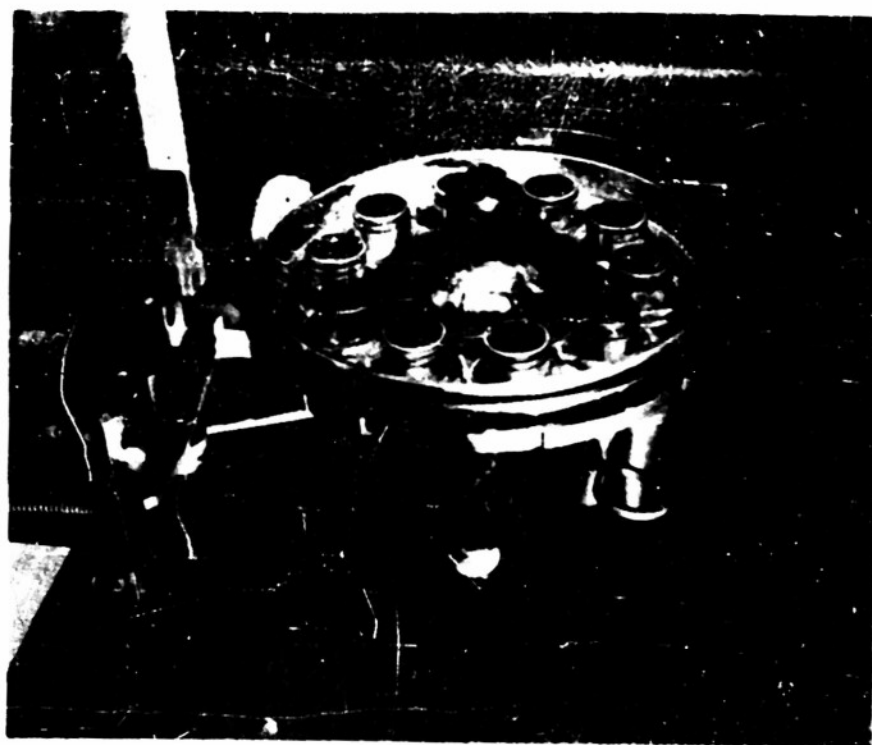


Fig. 1. Fractionating Disc

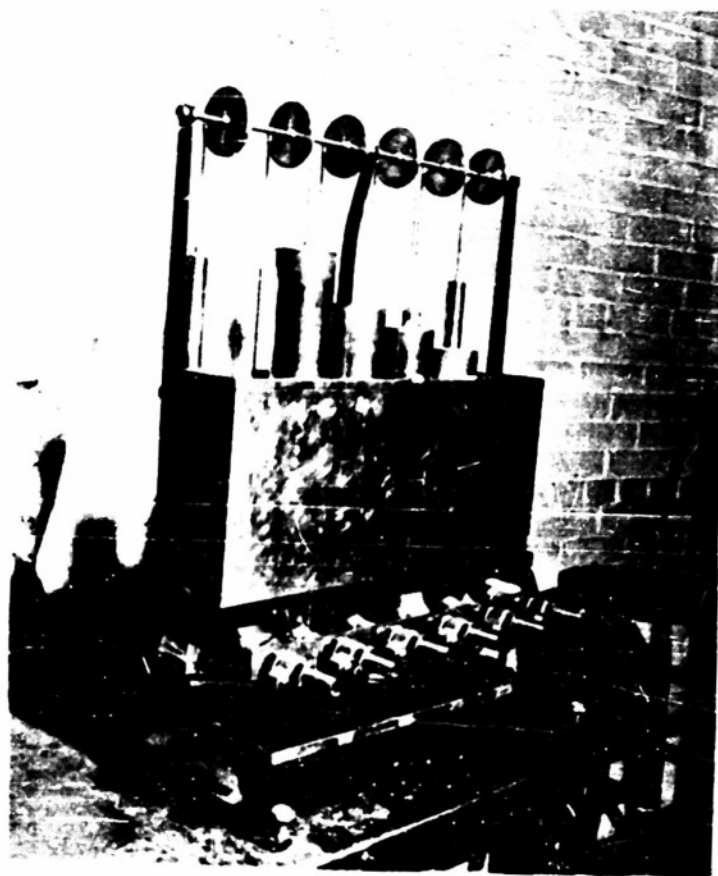


Fig. 2. Multiple Spirometer